Cont'd or mutant thereof.

49 (new). The method of claim 1 in which the disease is AIP ad the enzyme is PBGD or an enzymatically equivalent fragment thereof.

50 (new). The method of claim 1 in which the disease is AIP and the enzyme is PBGD.

51 (new). A method according to claim 1, wherein the catalyst is an enzymatically equivalent fragment or analogue of the enzyme and exerts at least part of its enzymatic activity intracellularly upon administration to the subject.

REMARKS

1. General Matters

1.1. Please note the change of address filed January 2, 2002 (copy enclosed).

1.2. The specification has been amended to provide a §120 reference only to PCT/DK99/00040 and 60/094,258. Since the declaration refers also to 09/358,856, we have filed an ADS. With regard to §120 priority, the ADS takes precedence over the declaration. This case is pre-AIPA, so the §120 amendment is timely.

1.3. The Examiner has failed to consider references AF or AN. I have checked our file and we did submit copies of these references; the citations appear to be in proper form.

We submit herewith our postcard receipt showing that they were filed, together with courtesy copies of them, and ask that they be considered without fee as the error was on the part of the PTO. If the next action relies on AF or AN, it should not be made "final".

1.4. The preliminary amendment of July 27, 2000 says that, in claim 20, replace "any of claims" with "claim". Claim 20 actually recited "any of the preceding claims". Applicants' clear intent was to eliminate multiple dependency; the

instructions contained an obvious typographical error. Since there is no doubt as to intent, see page 3 of the preliminary amendment, claim 20 should have been amended to replace "any of the preceding claims" with "claims". See MPEP §714.23.

1.5. The office action of November 6, 2001 lists claims 46 as pending but does not further characterize it as withdrawn, rejected or allowable. The confusion probably lies in that there were originally two claims numbered "36". So the second should have been renumbered "37", and then 37-45 renumbered as 38-46. Cp. office action mailed March 9, 2001.

Based on the latter, we believe that 46's status is "withdrawn".

1.6. We have noted that claim 40 ("39", as filed, but renumbered) is dependent on itself. This has been corrected.

2. Election/Restriction

2.1. A PBGD gene is known. On the group restriction, the Examiner's position is that since restriction between the gene and the protein per se would have been proper, restriction between a method of using the gene and a method of using the protein is likewise proper. The ISA/EPO and IPEA/EPO viewed the matter differently, and we agree with them.

While the gene was cloned, neither the claimed use of the gene nor the claimed use of the protein were taught by the prior art. These two claimed uses relate to a single general inventive concept under PCT Rule 13.1, as the use of the gene results, in vivo, in the production of the protein. There is a corresponding technical feature because neither method is obvious over the art.

2.2. On the species restriction, the Examiner's argument is ingenuous; we did not pay additional fees for more than one species to be examined because the ISA and IPEA did not make a species restriction.

3. Prior Art Issues

Claims 1-32 and 35-37 stand rejected as obvious over Raich (1986) (AI) in view of Beutler (1991).

Raich is said to teach (1) the gene encoding porphobilinogen deaminase (PBGD) and (2) that PBGD deficiency is responsible for acute intermittent porphyria (AIP).

The Examiner concedes that Raich did not teach enzyme replacement therapy of AIP, but argues that such therapy would have been obvious in view of the many publications on that generic technique, including Beutler (1991).

On point (2) above, Raich is parrotting the teachings of his reference (2), which is Meyer (1972). Thus, the connection between PBGD and AIP has been known since 1972, yet the existing therapies of AIP have been aimed at the first step in heme biosynthesis, mediated by ALA-synthetase. In particular, they aim at negative feedback regulation by increasing circulating heme (P4, L14-20). PBGD mediates a different step.

Plainly, enzyme replacement therapy has been known since 1991, the publication year of Beutler. We believe that replacement therapy has been known since 1966. See Feinstein RN et al.: Reversal of H_2O_2 toxicity in the acatalasemia mouse by catalase administration: Suggested model for possible replacement therapy of inborn errors of metabolism. J. Lab. Clin. Med. 68(6):952-7 (1966) (Ref. CH). Another early paper which includes the use of enzyme replacement therapy on humans is Brady RO et al.; Replacement therapy for inherited enzyme deficiency. Use of purified glucocerebrosidase in Gaucher's disease. N. Engl. J. Med. 291(19):989-93 (1974) (Ref. CE). (Copies of both papers are enclosed.) So why wasn't PBGD replacement therapy long ago attempted as a treatment for AIP?

The existence of a longfelt need for AIP therapy, coupled with the longterm failure of others to apply the concept of replacement therapy to AIP once Raich taught the PBGD/AIP

relationship, is objective evidence of nonobviousness.

4. Enablement

The Examiner concedes enablement for treatment of AIP by PBGD deficiency, but not for treatment of any disease caused by a deficiency in a heme biosynthesis pathway enzyme.

The heme biosynthetic pathway is well known (P1, L21-32; P7, L25-31; original claim 3). AIP is known to be mediated by a deficiency in one of the pathway enzymes, PBGD (P2, L8-12). A deficiency in AIP could also result from a deficiency in one of the other enzymes of the pathway, even if the PBGD step is normally the rate-limiting one. Such a causal relationship could be detected in a manner similar to that used to detect the AIP/PBGD relationship. The gross clinical manifestation would be the same (P2, L20-21), but the precursors to the step in question would be excreted in excess amounts, rather than the precursors (PBG and ALA) to the PBGD step.

With regard to diseases other than AIP which could arise from a heme biosynthetic pathway dysfunction, it is not unusual for claims to be allowed that are of the form "a method of treating a disease caused by X which comprises administering a therapeutically effective amount of the antagonist Y". New claim 47 requires that the disease be a porphyria, see P4, L11-14, P6, L26-28, original claim 2, and P38, L1-21.

5. Description

Claims 17 and 19-22 are rejected for lack of written description. These are original claims, and in general such claims are not properly so rejected.

In our opinion, this is really an enablement issue (indeed, at one point the Examiner argues that there is a lack of an "enabling description"). The distinction between enablement and description is important as, in adjudicating enablement, one may

consider what was well known in the art but not stated in the specification.

We now turn to the specific claims.

17: how is the catalyst's half life enhanced? We direct the examiner's attention to P13, L14-16 and claim 18 (PEG coating). Complexing with a heavy metal may also help, see P13, L17 and claim 19 (dependent on 17).

19: The examiner questions the failure to identify a specific heavy metal or how the complexing is to be achieved. Any person skilled in the art would be aware that there are only a limited number of heavy metals, and, of those, only a handful are tolerated by the body. Obvious candidates would be iron, copper, and zinc. It is difficult to perceive how achieving complexing is a problem.

21: The Examiner says that no "small artificial enzyme" or "organic catalyst that can polymerize porphobilinogen to hydroxymethylbilane" is described. However, enzymes are known to have multiple domains and, even within the enzymatic domain, it is not unusual to identify enzymatically active fragments. P13, L20 teaches that the catalyst may be an "enzymatically equivalent part" of an enzyme. See new claims 48 and 49.

The "organic catalyst" is a smaller organic molecule designed to possess the same catalytic activity as PBGD.

The present invention relates to methods of treating acute intermittent porphyria, a disease caused by an enzyme deficiency, by remedying that deficiency, i.e., providing the necessary catalytic activity. The natural enzyme, PBGD, has a particular catalytic activity. In theory, a nontoxic organic catalyst of synthetic origin could have the same activity. If so, it could be administered to the patient in place of PBGD. Applicants teach that such a substitution is possible, see P13, L22-24.

Applicants do not specifically teach any particular catalyst, nor do they assert that a PBGD-mimicking organic

catalyst is already known in the art. However, they teach that if and when such a catalyst becomes available, it may be used in their claimed method.

6. Definiteness

The Examiner questions the definiteness of several words or phrases, as discussed below.

"enzymatically equivalent part" (claims 1, 4, 5)

It appears that it would be sufficient to replace "part" with --fragment--. This has been done.

"analogue"

The Examiner acknowledges the use of the term on page 7, line 12 but says it does not define it. But it is clear from page 7, lines 13-16 that "enzymatically equivalent analogues" are molecules, other than the enzyme itself, which have the same specific enzymatic activity. The term "analogue" is used only in this context, not by itself. So it is definite.

"at least part of the
enzymatic activity" (claim 20)

Counsel is not sure he would call this a "relative phrase", but in any event relative phrases are not per se indefinite. The thrust of claim 20 is that it is not necessary that the activity be entirely intracellular, as long as intracellular activity is detectable. We consider this to be definite. We note that simply reciting that a catalyst is intracellularly active means that it is only intracellularly active.

For clarification, claim 20 has been cancelled and replaced with new claim 51.

"intracellularly"

(claim 20)

If unqualified, "intracellularly" necessarily means, within any cell of the body. This is definite.

Claim 20 has been replaced by claim 51.

"tagged with specific carbohydrates" (claim 23)

We are not sure whether the objection is to "tagged" or to "specific carbohydrates". It is well known that liver cells have surface carbohydrate receptors and will internalize molecules with matching carbohydrates. So the claim language appears proper.

"other liver cell specific structures" (claim 23)

Liver cells have other surface receptors, too. Claim 23 has been amended to recite "tagged with a ligand specifically recognized by a liver cell whereby the tagged molecule is intemalized by the liver cell".

22: The Examiner complains that the specification does not explain how to formulate the catalyst so as to have intracellular activity. But that is not true, at least if "formulate" is broadly construed. See P8, L31 to P9, L9, and original claim 23.

We are not persuaded of the difference the examiner is urging between "stating" or "suggesting" something, and "describing" it.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosures
-ADS
-postcard receipt for IDS
-courtesy copies of refs AF and AN
-Feinstein (1966)
-Brady (1974)
-Change of Address

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\BN\P\Plou\fogh1\ptoamend1.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 20 has been cancelled.

Claims 47-51 have been added.

Claims 1, 3, 4, 5, 21, 23, and 40 have been amended as follows:

1 (amended). A method for treatment or prophylaxis of disease caused by deficiency, in a subject, of an enzyme belonging to the heme biosynthetic pathway, the method comprising administering, to the subject, an effective amount of a catalyst which is said enzyme or an enzymatically equivalent [part] fragment or analogue thereof.

3 (amended). A method according to claim 1, wherein the catalyst is an enzyme selected from the group consisting of
porphobilinogen deaminase (PBGD)
ALA dehydratase,
Uroporphyrinogendecarboxylase,
Coproporphyrinogen oxidase,
Coproporphyrinogen oxidise,
Protoporphyrinogen oxidase,
Uroporphyrinogen III synthase,
Ferrochelatase, and
Uroporphyrinogen decarboxylase,
or an enzymatically equivalent [part] fragment or analogue thereof.

4 (amended). A method according to claim 1, wherein the disease is AIP and the enzyme is PBGD or an enzymatically equivalent [part] fragment or analogue thereof.

5 (amended). A method according claim 1, wherein the catalyst is a recombinant form of the enzyme belonging to the heme biosynthetic pathway or of the enzymatically equivalent [part] fragment or analogue thereof.

21 (amended). A method according to claim [20] 51, wherein the catalyst is a small artificial enzyme or an organic catalyst which can polymerize porphobilinogen to hydroxymethylbilane.

23 (amended). A method according to claim 22, wherein the catalyst is tagged with a ligand specifically recognized by a liver cell whereby the tagged molecule is internalized by the liver cell [specific carbohydrates or other liver cell specific structures for specific liver uptake].

40 (amended). The method according to claim [40] 39 wherein the disease is Acute Intermittent Porphyria, (AIP).

G:\BN\P\Plou\fogh1\ptoamend1.wpd